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CYTOLYTIC LYMPHOCYTES *and* COMPLEMENT: EFFECTORS *of the* IMMUNE SYSTEM

Volume I

Eckhard R. Podack

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Cytolytic Lymphocytes and Complement: Effectors of the Immune System

Volume I

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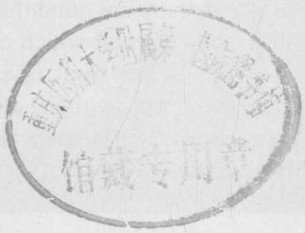
Dedication

To my father, Dr. med. Waldemar W. Podack, in gratitude for stimulating my interest in science.



INTRODUCTION

These volumes, *Cytolytic Lymphocytes and Complement: Effectors of the Immune System,* originate from the realization that pathways of recognition and killing of foreign targets follow similar routes in the humoral and cellular part of the immune system. In particular, the homology of immunoglobulins with the T-cell-MHC-antigen receptor at the beginning of the recognition sequence and the homology of complement component C9 with lymphocyte perforin 1 (P1) as pore formers at the end of the effector sequence are striking examples.

From my own point of view, the catalyst for suspecting mechanistically similar pathways in the effector systems of complement and cytolytic lymphocytes derived from the discovery of the polymerization of C9 to the circular structure of poly C9 (see Figure 1), which is responsible for the well-known ultrastructural complement lesions described originally in 1964. This simple finding immediately clarified conceptually the mechanisms for the formation of transmembrane pores both by complement and by cytolytic T- and NK-cells.

The motivation to assemble these volumes through the contributions of outstanding investigators in complement and lymphocyte research thus was, and is, to increase the awareness that mechanisms and molecular models studied in one system may well be of relevance to the other. Since complement has been studied in detail in all of its aspects, including activation, host protection, cytolysis, and repair mechanisms, it can serve as a guiding model system for the investigator of cellular mechanisms.

Effector cells, on the other hand, have the facility to interact with targets through surface membrane receptors allowing them an additional degree of complexity compared to humoral systems. This complexity, combined with the subcellular organization of cells (for example, the sequestration of cytolytic proteins in granules), offers alternatives for the mediation and regulation of cellular pathways that can be quite different from the humoral pathway.

Owing to these differences, the approaches to the use of the two effector systems for immune therapy are quite distinct. However, both are being explored at this time, and only future work will tell which combination of immune therapy will be most effective.

It is one of the most fascinating aspects of research to experience the development of common concepts with the attendant simplifications and understanding at the molecular level of previously poorly understood phenomena. It is hoped that this book will contribute to this process.

E. R. Podack

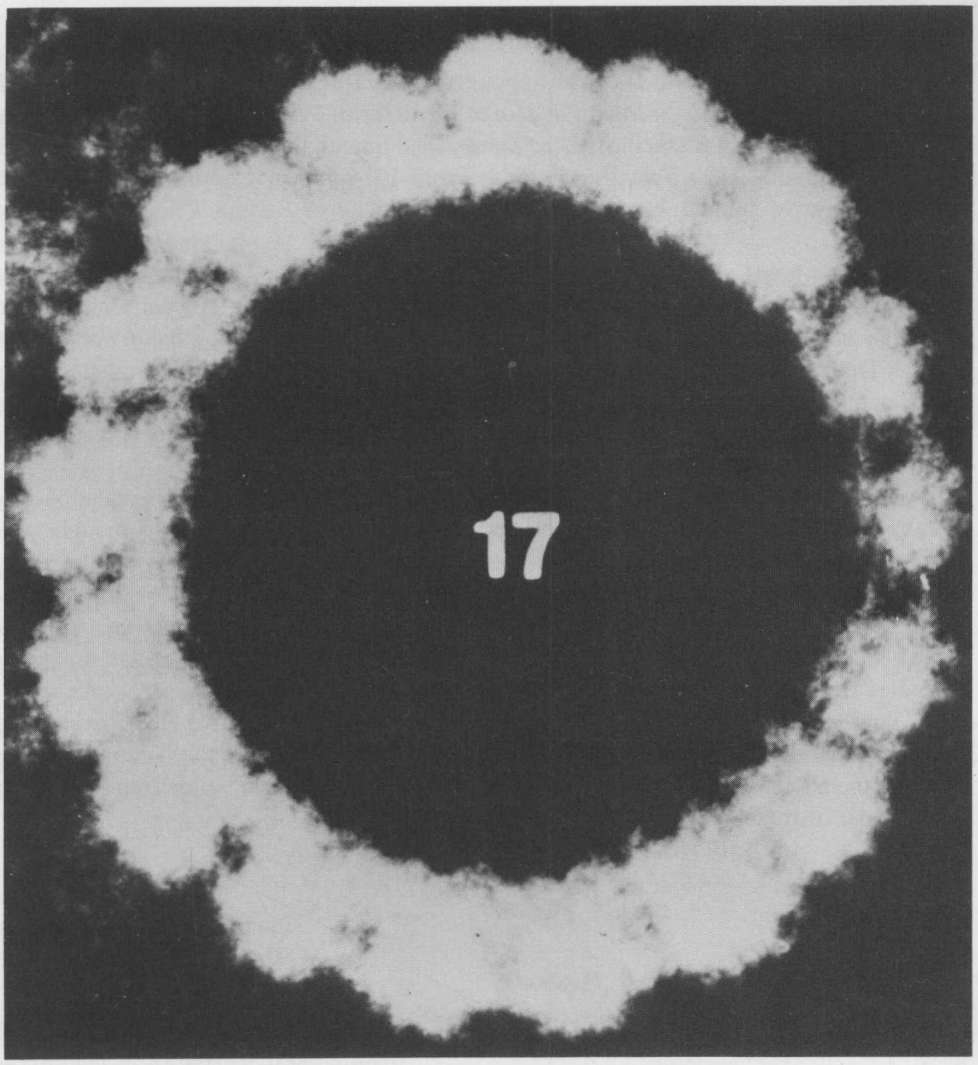


FIGURE 1. Poly C9.

THE EDITOR

Eckhard R. Podack, M. D., was appointed Full Professor of Microbiology and Immunology at the University of Miami School of Medicine in 1987. Prior to this appointment, he had been Professor of Medicine, Microbiology, and Immunology at the New York Medical College in Valhalla, New York, since 1984. From 1974 to 1984, he was associated with the Department of Immunology at the Research Institute of Scripps Clinic in La Jolla, California.

Dr. Podack holds the M.D. from Johann-Wolfgang-Goethe University in Frankfurt, Germany, and wrote his dissertation in Biochemistry at the Georg August University of Göttingen in Germany. His research thesis was honored with the Annual Award by the German Diabetes Society in 1973. Post-doctoral fellowship training was completed in the Department of Biochemistry at the University of Göttingen before he moved to this country in 1974. In biochemistry and immunology, Dr. Podack is internationally recognized and is a frequent invited lecturer to universities in Europe and the United States.

After collaborating with Hans Müller-Eberhard at the Scripps Research Foundation from 1974 to 1978 on complement components and activation, he spent the next six to eight years studying independently the molecular biology of molecules that cytotoxic lymphocytes use to kill their targets.

Dr. Podack is the recipient of two National Institutes of Health grants, an American Cancer Society grant, two Fellowship grants for his Post-Doctoral fellows, and a proposal of studies from private industry.

Dr. Podack is Associate Editor of the *Journal of Immunology* and Ad Hoc Reviewer for nine additional scientific journals. He reviews grant applications for the Veterans Administration, the National Science Foundation, the Fogarty International Fellowship Center, and the National Institutes of Health.

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Section I.A: Recognition — Complement

Chapter 1

C1 STRUCTURE AND ANTIBODY RECOGNITION

Verne N. Schumaker

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I. INTRODUCTION

This chapter will focus upon the remarkable structure of the first component of complement, C1, and upon its interactions with C1-inhibitor and with antibody. A comprehensive review of C1 has just appeared;[17] therefore, we will concentrate on experimental studies published after the writing of that review and a hypothetical, but particularly satisfying, model for the structure of C1, variants of which have been proposed by three different laboratories.

Reviews which discuss the early components of the classical pathway, especially C1 and C1q, have been written by Cooper,[17] Lachmann and Hughes-Jones,[44] Colomb et al.,[15,16] Ziccardi,[94] Reid,[66] Loos,[47] and Porter and Reid,[61,67] among others.

The destruction and elimination of bacteria, virus, and toxins by the humoral arm of the immune system involves antibody molecules, phagocytic cells, and the alternate and classical pathways as well as the membrane attack complex of complement.[43,50] Activation of either complement pathway results in the release of anaphylatoxic peptides causing increased vascular permeability, smooth muscle contraction, release of histamine from mast cells, and chemotaxis of phagocytes to the site of infection;[34,35] as well as the deposition of potent opsonins such as C3b[54,99] and activation of the terminal components which assemble to mount a direct attack on the membrane of the invader[7,51] (and see Chapter 10, this volume).

Immune complexes composed of IgM and IgG as well as certain bacterial and viral cell wall materials, are included among the strong activators of the classical pathway. Individuals deficient in the early components of the classical pathway, C1q, C1r, C2 and C4, are only occasionally more vulnerable to bacterial and viral infection;[1] presumably, the alternate pathway can usually provide the critical defense effector functions, as it must prior to the development of effective levels of antibody in a naive host. Deficient individuals appear to be susceptible to immune-complex-associated renal diseases;[12,26,80] thus, the early components may play an important role in the solubilization and elimination of immune complexes.

The key role of immune complex recognition and initiation of the classical pathway is the principle function of the first component of complement. We will begin with an overview to illustrate the probable structures of the macromolecules involved, the names of some of their component parts, and what is meant by the "recognition" and "initiation" processes.

II. MULTIVALENT ATTACHMENT OF C1 TO A CLUSTER OF ANTIBODY Fc INITIATES THE CLASSICAL COMPLEMENT PATHWAY

Immune complex recognition is accomplished by the binding of C1 to a cluster of antibody Fc, as schematically illustrated in Figure 1, and its subsequent activation[71,98] C1 is a complex composed of five protein subcomponents: one C1q, two C1r and two C1s.[89] The C1q subcomponent is a fascinating macromolecule, consisting of a central "stem" with six branching "arms", each arm terminating in a globular C1q "head".[61] The heads bind to complementary regions on the Fc domains of IgG and IgM. Since the binding of a single head to a single Fc is weak, tight binding of C1q to an immune complex requires multivalent attachment to a cluster of Fc, as illustrated in Figure 1.[98,106]

Binding of C1 to immune complexes is usually followed by a slower activation step in which most of the bound C1 becomes proteolytically active. Activation involves the other subcomponents; the two C1r and two C1s subcomponents are shown in Figure 1 as a string of balls wound among the C1q arms. C1r and C1s are proenzymes, and activation involves proteolytic cleavage of the C1r polypeptide. The activated C1r then cleaves C1s which, in turn, cleaves the next components in the classical pathway, C4 and C2, to initiate the classical component cascade.[86]

Not only can C1 activate by binding multivalently to an immune complex, but also C1